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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/828,986	04/20/2004	Michael T. Barrett	10031482-1	7617

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EXAMINER	
SHAW, AMANDA MARIE	
ART UNIT	**PAPER NUMBER**
1634	

NOTIFICATION DATE	DELIVERY MODE
02/29/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

IPOPS.LEGAL@agilent.com

Office Action Summary	Application No.	Applicant(s)	
	10/828,986	BARRETT ET AL.	
	Examiner	Art Unit	
	AMANDA SHAW	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31 and 34* is/are pending in the application.

4a) Of the above claim(s) *7-24,30 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 25-29, and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed November 30, 2007. This action is made FINAL.

Claims 1-31 and 34 are currently pending. Claims 7-24 and 30-31 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Claims 1-6, 25-29, and 34 will be addressed herein.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang (US Patent 6605432 Filed 2000) in view of Yakhini (EP 1288313 Published 3/2003).

Regarding Claim 1 Huang teaches an array comprising CpG dinucleotide rich probes. These CpG dinucleotide rich probes affixed to the solid support of the screening array are employed to identify the presence or absence of methylated sites (Column 7, lines 8-51). Huang also teaches stringent assay conditions. Specifically Huang teaches hybridization was carried out overnight at 65 ºC in 10 ml of high efficiency hybridization solution. Washing was preformed once for 20 min in 0.1% SDS-0.5xSSC and twice for 20 min each in 0.1% SDS-0.2xSSC at 65º to 75º C (Column 19 lines 43-50).

Huang does not teach that the CpG probes contain at least one unstructured nucleic acid.

However Yakhini teaches an array of probes comprising unstructured nucleotides. Yakhini further teaches that these probes have a reduced ability to hybridize to each other as compared to nucleic acid probes with naturally occurring nucleotides (Para 0014).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the array of probes taught by Huang by changing the probes of Huang so that the modified probes contain at least one

unstructured nucleic acid as suggested by Yakhini. The probes of Yakhini allow for the reduction of cross hybridization between the probes on the array. This is beneficial because cross hybridization can lead to false signals and reduce the number of probes on the array available to bind to the target (Para 0014). Thus modifying the probes of Huang would have allowed for a more effective means for detecting CpG sites.

Regarding Claim 2 Huang further teaches a method wherein the CpG probe binds to an uncleaved CpG island but not to a CpG island cleaved by a methylation sensitive restriction enzyme. Specifically Huang teaches subjecting a nucleic acid sample to a methylation sensitive restriction enzyme which digests unmethylated CpG sites leaving methylated CpG sites in tact, amplifying the methylated CpG fragments, and hybridizing the amplicons to the CpG probe array. Amplicons which are complementary to the probe sequences on the CpG array will produce a positive hybridization signal (column 14, lines 8-67).

Regarding claims 3 and 4 Huang does not teach a method wherein the UNA comprises nucleotides G' and C' wherein G' and C' base pair with each other with a stability that is lower than that of G and C. Further Huang does not teach a method wherein the UNA comprises nucleotides A' and T' wherein A' and T' base pair with each other with a stability that is lower than that of A and T.

However the UNA probes of Yakhini have a reduced ability to form stable hydrogen bonded with base pair (Para 0027). Thus Yakhini teach a method wherein the UNA comprises nucleotides G' and C' wherein G' and C' base pair with each other with a stability that is lower than that of G and C. Further Huang does not teach a

method wherein the UNA comprises nucleotides A' and T' wherein A' and T' base pair with each other with a stability that is lower than that of A and T.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the array of probes taught by Huang by changing the probes of Huang so that the modified probes contain at least one unstructured nucleic acid as suggested by Yakhini. The probes of Yakhini allow for the reduction of cross hybridization between the probes on the array. This is beneficial because cross hybridization can lead to false signals and reduce the number of probes on the array available to bind to the target (Para 0014). Thus modifying the probes of Huang would have allowed for a more effective means for detecting CpG sites.

Regarding Claim 5 Huang teaches an array of CpG probes (Abstract).

Regarding Claim 6 Huang teaches an array containing at least 1000 different probes (Column 9, lines 61-64).

4. Claims 25-29 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang (US Patent 6605432 Filed 2000) in view of Yakhini (EP 1288313 Pub 3/2003) and in further view of Ahern (The Scientist 1995).

The teachings of Huang and Yakhini are presented above.

Regarding Claim 25 the combined references do not teach a kit comprising a CpG oligonucleotide.

However, reagent kits for performing hybridization assays were conventional in the field of molecular biology at the time the invention was made. In particular, Ahern discloses the general concept of kits for performing detection methods and teaches that

kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Ahern (page 22) also teaches that kits provide the benefits of cost-effectiveness and time efficiency. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the CpG UNA array and instructions for its use into a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art wishing to detect CpG methylation.

Regarding Claim 26 Huang teaches that the probes are attached to an array (Abstract). Therefore Huang teaches a method wherein the oligonucleotide is surface bound.

Regarding Claim 27 Huang teaches that the probes are attached to an array (Abstract). Therefore Huang teaches a method wherein the oligonucleotide is present on an array of features.

Regarding Claim 29 the combined references do not teach that the kit further comprising reagents for labeling the samples. However Huang teaches that the samples are labeled (Column 14, line 42).

However, reagent kits for performing hybridization assays were conventional in the field of molecular biology at the time the invention was made. In particular, Ahern discloses the general concept of kits for performing detection methods and teaches that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Ahern (page 22) also teaches that kits provide the benefits of cost-effectiveness

and time efficiency. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to included labeling reagents in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art wishing to detect CpG methylation.

It is further noted that Claims 28 and 34 have been amended to recite particular instructions to include in the kits. Printed matter in kits such as instructions are not given any patentable weight. Please refer to MPEP 2112.02 III.

5. Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang (US Patent 6605432 Filed 2000) in view of Kutyavin et al (US Patent 5912340 Issued 1999).

Regarding Claims 1-6 Huang teaches an array comprising CpG dinucleotide rich probes. These CpG dinucleotide rich probes affixed to the solid support of the screening array are employed to identify the presence or absence of methylated sites (Column 7, lines 8-51). Huang further teaches a method comprising: subjecting a nucleic acid sample to a methylation sensitive restriction enzyme which digests unmethylated CpG sites leaving methylated CpG sites in tact, amplifying the methylated CpG fragments, and hybridizing the amplicons to the CpG probe array. Amplicons which are complementary to the probe sequences on the CpG array will produce a positive hybridization signal (column 14, lines 8-67).

Huang does not teach that the CpG probes contain at least one unstructured nucleic acid.

However Kutyavin et al teach probes which contain unstructured nucleic acids (Abstract and Table 2). Specifically Kutyavin et al teach probes which comprise nucleotides G' (6-oxo-purine (hypoxanthine)), C' (pyrrolo-[2,3-d]pyrimidine-2(3H), A' (2-aminoadenine) and T' (2-thiothymine). The modified bases are capable of forming a stable base pair with their natural base partner, but are unable to form a stable base pair with their modified base partner (Abstract, Columns 6-8). Thus Kutyavin et al teach that G' and C' and A' and T' base pair with each other at a stability that is lower than that of G and C and A and T.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the array of probes taught by Huang by changing the probes of Huang so that the modified probes contain at least one unstructured nucleic acid as suggested by Kutyavin et al. The probes of Kutyavin allow for the reduction of the formation of secondary structures between adjacent probes which can interfere with the hybridization between the probe and the target. Thereby modifying the probes of Huang would have allowed for a more effective means for detecting CpG sites.

6. Claims 25-29 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang (US Patent 6605432 Filed 2000) in view of Kutyavin et al (US Patent 5912340 Issued 1999) and in further view of Ahern (The Scientist 1995).

The teachings of Huang and Kutyavin et al are presented above.

Regarding Claims 25-29 and 34 the combined references teach an array comprising CpG UNA probes. Further Huang teaches a method comprising contacting

sample nucleic acid with a methylation sensitive restriction enzyme to produce a target composition and assessing the binding of said target to the probe array (Column 14, lines 8-66). Additionally Huang further teaches a method comprising contacting a control nucleic acid (derived from a non cancer cell) and a test nucleic acid (derived from a cancer cell) with a methylation sensitive restriction enzyme to produce a first and second set of target compositions, contacting the first set of target compositions to a first array, contacting the second set of target compositions to a second array, and comparing the binding between both sets (column 16, lines 53-58).

However the combined references do not teach packaging the CpG UNA array and instructions for its use into a kit. However, reagent kits for performing hybridization assays were conventional in the field of molecular biology at the time the invention was made. In particular, Ahern discloses the general concept of kits for performing detection methods and teaches that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Ahern (page 22) also teaches that kits provide the benefits of cost-effectiveness and time efficiency. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the CpG UNA array and instructions for its use into a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art wishing to detect CpG methylation.

Additionally it is noted that claims 28 and 34 have been amended to recite particular instructions to include in the kits. Printed matter in kits such as instructions are not given any patentable weight. Please refer to MPEP 2112.02 III.

Response To Arguments

7. In the response filed November 30, 2007, the Applicants traversed the rejections made over Huang in view of Yakhini and Huang in view of Kutyavin. The first argument is that Huang provides no reason to modify his probes to contain a UNA nucleotide; therefore the Applicants believe that motivation does not exist to combine Huang with Yakhini or Kutyavin. Here it is noted for the record that KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. See the recent Board decision Ex parte Smith, --USPQ2d--, slip op. at 20, (Bd. Pat, App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396) (http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf). Nonetheless motivation is present and is provided. The benefits of using unstructured nucleic acid probes are specifically taught by Yakhini and Kutyavin and one would have been motivated to combine the teachings of Huang with Yakhini or Kutyavin in order to take advantage of these benefits. For example Yakhini teaches that probes which comprise unstructured nucleic acids have a reduced ability to hybridize to each other and to themselves as compared to nucleic acid with naturally occuring nucleotides. Yakhini teaches that using probes with unstructured nucleic acids reduces the cross hybridization between potentially complementary probe molecules. This form of cross

hybridization leads to false signals and reduces the amount of available probes in the assay for proper target detection and identification. Kutyavin also teaches that unstructured nucleic acids are capable of forming a stable base pair with their natural base partner, but are unable to form a stable base pair with their modified base partner (Abstract, Columns 6-8). In the instant case all of the claimed elements were known in the prior art. The only difference is the combination of the claimed elements. Combining prior art elements to yield predictable results is considered obvious.

The Applicants further argue that Huang probes are very long and PCR generated and thus not synthesizable using UNA nucleotides. The specification (col 13, lines 28-30) teaches that "the endonuclease restricted amplicons are then amplified, **preferably** using PCR". Although PCR is a preferred embodiment, this teaching is not limited to PCR and could encompass other types of nucleic acid synthesis such as chemical synthesis. This is supported by the MPEP 2123 which states that a reference should be considered for all that it teaches including nonpreferred embodiments. In the instant case methods of chemically synthesizing probes were well known in the art at the time of the invention. Further it is noted that the claims do not require the probes of the array to be synthesized in any particular way.

The Applicants further state that in their prior response they made the argument that since Huang relies on PCR methods for amplifying genome samples, there would be no need to increase hybridization efficiency. The Applicants point to the specification (col 13, lines 28-30) which states that "the endonuclease restricted amplicons are then amplified, preferably using PCR" for support. However, it is unclear how this recitation

provides support for the assertion that when an array is made of PCR generated probes there is never a need to increase hybridization efficiency. For these reasons the rejections made over Huang in view of Yakhini and Huang in view of Kutyavin are maintained.

The response also traversed the rejection made over Huang in view of Yakhini and in further view of Ahern and the rejection made over Huang in view of Kutyavin and in further view of Ahern. The Applicants main argument is that Ahern fails to meet the deficiencies of Huang and Yakhini and Huang and Kutyavin. The examiner disagrees for the reasons presented above. The only limitation that is not taught by the combined teachings of Huang and Kutyavin is packaging the CpG UNA array and instructions for its use into a kit. However Ahern teaches why it would be obvious to do this. For these reasons the rejection made over Huang in view of Yakhini and in further view of Ahern and the rejection made over Huang in view of Kutyavin and in further view of Ahern are maintained.

Conclusion

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

/Juliet C Switzer/

Primary Examiner, Art Unit 1634